Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
30th Prioritization – 1st quarter 2017

General Information, efficacy and safety data

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Please note:

Within this document you find general information about the drug of interest and the indication it is intended to be used for. Further we have included full text publications and conference abstracts of phase III trials, assessing the safety and efficacy of the drugs of interest.

At the very end of each chapter we have provided a table containing the prioritization criteria and a drop-down field to apply the provided criteria.

Introduction

As part of the project „Horizon Scanning in Oncology“ (further information can be found here: http://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie), 9 information sources are scanned frequently to identify emerging anticancer drugs.

Every 3 months, these anticancer therapies are filtered (i.e. in most cases defined as availability of phase III results; for orphan drugs also phase II) to identify drugs at/around the same time as the accompanying drug licensing decisions of the EMA.

An expert panel consisting of oncologists and pharmacists then applies 5 prioritisation criteria to elicit those anti-cancer therapies which might be associated with either a considerable impact on financial resources or a substantial health benefit.

For the 30 prioritisation (February 2017), 12 drugs were filtered out of 301 identified and were sent to prioritisation. Of these, 5 drugs were ranked as ‘highly relevant’ by the expert panel, 7 as ‘relevant’ and 0 as ‘not relevant’. For ‘highly relevant’ drugs, further information including, for example, abstracts of phase III studies and licensing status is contained in this document.

The summary judgements of the expert panel for all prioritised drugs are provided in the following table.

No	Filtered Drugs – 30th prioritisation 1st quarter 2017	Overall category
1.	Atezolizumab (Tecentriq®) versus docetaxel in patients with previously treated non-small-cell lung cancer	Highly relevant
2.	Cabozantinib (Cabometyx®) versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk	Relevant
3.	Nivolumab (Opdivo®) in metastatic urothelial carcinoma after platinum therapy	Relevant
4.	Pembrolizumab (Keytruda®, MK-3475) as second-line therapy for advanced urothelial carcinomas	Highly relevant
5.	Daratumumab (Darzalex®), bortezomib, and dexamethasone for multiple myeloma	Highly relevant
6.	Bortezomib (Velcade®) with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant	Highly relevant
7.	Trastuzumab emtansine (Kadcyla®) with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2–positive, advanced breast cancer	Relevant
8.	Utidelone plus capecitabine versus capecitabine alone for heavily pretreated metastatic breast cancer refractory to anthracyclines and taxanes	Relevant
9.	Rucaparib (Rubraca®) in relapsed, platinum-sensitive high-grade ovarian carcinoma	Relevant
10.	Niraparib (MK-4827) maintenance therapy in platinum sensitive, recurrent ovarian cancer	Relevant
11.	Prolonged survival in stage III melanoma with ipilimumab (Yervoy®) adjuvant therapy	Highly relevant
12.	Regorafenib (Stivarga®) for patients with hepatocellular carcinoma who progressed on sorafenib treatment	Relevant

1 Lung cancer

1.1 Atezolizumab (Tecentriq®) versus docetaxel in patients with previously treated non-small-cell lung cancer

Overview

Drug Description		a programmed death-ligand 1 (PD-L1) blocking antibody
Patient Indication		atezolizumab for previously treated non-small-cell lung cancer
Incidence in Austria		4,716 newly diagnosed per year (2014), 56.9/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT01903993 until 02/2017 NCT02008227 until 12/2017
Approval status for this indication	**EMA**	-
	FDA	10/2016: metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy
Approval status for other indications	**EMA**	-
	FDA	05/2016: for the treatment of patients with locally advanced or metastatic urothelial carcinoma who: • have disease progression during or following platinum-containing chemotherapy • have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Costs		-

Phase III results

Lancet (2017), published online December 12, 2016 (Rittmeyer et al.) *"Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial"*

Background
Atezolizumab is a humanised antiprogrammed death-ligand 1 (PD-L1) monoclonal antibody that inhibits PD-L1 and programmed death-1 (PD-1) and PD-L1 and B7-1 interactions, reinvigorating anticancer immunity. We assessed its efficacy and safety versus docetaxel in previously treated patients with non-small-cell lung cancer.

Methods
We did a randomised, open-label, phase 3 trial (OAK) in 194 academic or community oncology centres in 31 countries. We enrolled patients who had squamous or non-squamous non-small-cell lung cancer, were 18 years or older, had measurable disease per Response Evaluation Criteria in Solid Tumors, and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients had received one to two previous cytotoxic chemotherapy regimens (one or more platinum based combination therapies) for stage IIIB or IV non-small-cell lung cancer. Patients with a history of autoimmune disease and those who had received previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway were excluded. Patients were randomly assigned (1:1) to intravenously receive either atezolizumab 1200 mg or docetaxel 75 mg/m2 every 3 weeks by permuted block randomisation (block size of eight) via an interactive voice or

web response system. Coprimary endpoints were overall survival in the intention-to-treat (ITT) and PD-L1-expression population TC1/2/3 or IC1/2/3 (≥1% PD-L1 on tumour cells or tumour-infiltrating immune cells). The primary efficacy analysis was done in the first 850 of 1225 enrolled patients. This study is registered with ClinicalTrials.gov, number NCT02008227.

Findings
Between March 11, 2014, and April 29, 2015, 1225 patients were recruited. In the primary population, 425 patients were randomly assigned to receive atezolizumab and 425 patients were assigned to receive docetaxel. Overall survival was significantly longer with atezolizumab in the ITT and PD-L1-expression populations. In the ITT population, overall survival was improved with atezolizumab compared with docetaxel (median overall survival was 13·8 months [95% CI 11·8–15·7] vs 9·6 months [8·6–11·2]; hazard ratio [HR] 0·73 [95% CI 0·62–0·87], p=0·0003). Overall survival in the TC1/2/3 or IC1/2/3 population was improved with atezolizumab (n=241) compared with docetaxel (n=222; median overall survival was 15·7 months [95% CI 12·6–18·0] with atezolizumab vs 10·3 months [8·8–12·0] with docetaxel; HR 0·74 [95% CI 0·58–0·93]; p=0·0102). Patients in the PD-L1 low or undetectable subgroup (TC0 and IC0) also had improved survival with atezolizumab (median overall survival 12·6 months vs 8·9 months; HR 0·75 [95% CI 0·59–0·96]). Overall survival improvement was similar in patients with squamous (HR 0·73 [95% CI 0·54–0·98]; n=112 in the atezolizumab group and n=110 in the docetaxel group) or non-squamous (0·73 [0·60–0·89]; n=313 and n=315) histology. Fewer patients had treatment-related grade 3 or 4 adverse events with atezolizumab (90 [15%] of 609 patients) versus docetaxel (247 [43%] of 578 patients). One treatment-related death from a respiratory tract infection was reported in the docetaxel group.

Interpretation
To our knowledge, OAK is the first randomised phase 3 study to report results of a PD-L1-targeted therapy, with atezolizumab treatment resulting in a clinically relevant improvement of overall survival versus docetaxel in previously treated non-small-cell lung cancer, regardless of PD-L1 expression or histology, with a favourable safety profile.

2 Urothelial carcinoma

2.1 Pembrolizumab (Keytruda®, MK-3475) as second-line therapy for advanced urothelial carcinomas

Overview

Drug Description		a human programmed death receptor-1 (PD-1)-blocking antibody
Patient Indication		pembrolizumab for metastatic or surgically unresectable urothelial carcinoma whose disease progressed or recurred despite previous treatment with at least one platinum-based chemotherapy regimen
Incidence in Austria		1,427 newly diagnosed per year (2014), 17.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02256436 - until 01/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	07/2015: pembrolizumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults 07/2016: pembrolizumab for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations

		prior to receiving pembrolizumab
	FDA	09/2014: patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor 10/2016: • Patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] greater than or equal to 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC • Patients with metastatic NSCLC whose tumors express PD-L1 (TPS greater than or equal to 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab 08/2016: for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy
Costs		pembrolizumab 50 mg: € 1,812.55 - patients received 200 mg every 3 weeks (€7,250.2)

Phase III results

NEJM (2017), published online February 17, (Bellmunt et al.) *"Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma"*

Background
Patients with advanced urothelial carcinoma that progresses after platinum-based chemotherapy have a poor prognosis and limited treatment options.

Methods
In this open-label, international, phase 3 trial, we randomly assigned 542 patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy to receive pembrolizumab (a highly selective, humanized monoclonal IgG4κ isotype antibody against programmed death 1 [PD-1]) at a dose of 200 mg every 3 weeks or the investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine. The coprimary end points were overall survival and progression-free survival, which were assessed among all patients and among patients who had a tumor PD-1 ligand (PD-L1) combined positive score (the percentage of PD-L1–expressing tumor and infiltrating immune cells relative to the total number of tumor cells) of 10% or more.

Results
The median overall survival in the total population was 10.3 months (95% confidence interval [CI], 8.0 to 11.8) in the pembrolizumab group, as compared with 7.4 months (95% CI, 6.1 to 8.3) in the chemotherapy group (hazard ratio for death, 0.73; 95% CI, 0.59 to 0.91; P=0.002). The median overall survival among patients who had a tumor PD-L1 combined positive score of 10% or more was 8.0 months (95% CI, 5.0 to 12.3) in the pembrolizumab group, as compared with 5.2 months (95% CI, 4.0 to 7.4) in the chemotherapy group (hazard ratio, 0.57; 95% CI, 0.37 to 0.88; P=0.005). There was no significant between-group difference in the duration of progression-free survival in the total population (hazard ratio for death or disease progression, 0.98; 95% CI, 0.81 to 1.19; P=0.42) or among patients who had a tumor PD-L1 combined positive score of 10% or more (hazard ratio, 0.89; 95% CI, 0.61 to 1.28; P=0.24). Fewer treatment-related adverse events of any grade were reported in the pembrolizumab group than in the chemotherapy group (60.9% vs. 90.2%); there were also fewer events of grade 3, 4, or 5 severity reported in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4%).

Conclusion
Pembrolizumab was associated with significantly longer overall survival (by approximately 3 months) and with a lower rate of treatment-related adverse events than chemotherapy as second-line therapy for platinum-refractory advanced urothelial carcinoma. (Funded by Merck; KEYNOTE-045 ClinicalTrials.gov number, NCT02256436.)

3 Multiple Myeloma

3.1 Daratumumab (Darzalex®), bortezomib, and dexamethasone for multiple myeloma

Overview

Drug Description		human CD38-directed monoclonal antibody (CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells)
Patient Indication		daratumumab in combination with bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma.
Incidence in Austria		382 newly diagnosed per year (2014), 4.3/100,000/year (European Standard Population, 2013)
Ongoing Phase III		NCT02136134 - until 03/2017
Approval status for this indication	**EMA**	-
	FDA	11/2016: in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy
Approval status for other indications	**EMA**	05/2016: approved as a monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. On 17 July 2013, orphan designation was granted by the European Commission to Janssen-Cilag International N.V., Belgium, for daratumumab for the treatment of plasma-cell myeloma.
	FDA	11/2015: approved for the administration as a single agent for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.
Costs		1 cycle → 21 days <u>Dexamethasone:</u> in one treatment cycle a dosis of 20 mg was administered 8 times → total of 160 mg; 100 mg → €28.70 and for 160 mg costs of €45.92 would incur for 1 treatment cycle <u>Bortezomib</u>: 1.3 mg/square meter body surface administered (subcutaneously) 4 times per treatment cycle; 3.5 mg → €1,218.95 assuming a body surface of 1.70 m^2, 2.21 mg (€769.68) are needed per administration and for 1 treatment cycle costs of €3,078.7 would incur <u>Daratumumab:</u> 16 mg/kg/once per week (intravenously); 400 mg → €2,209.45; assuming an average body weight of 70 kg, 1,120 mg are needed per week and 3,360 mg are needed for 3 weeks; costs of €18,559.38 would incur for 1 treatment cycle Total costs of €21,684 for 1 treatment cycle of combination treatment would incur

Phase III results

NEJM (2016) 375:754-766 (Palumbo et al.): *"Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma"*

Background
Daratumumab, a human IgGκ monoclonal antibody that targets CD38, induces direct and indirect antimyeloma activity and has shown substantial efficacy as monotherapy in heavily pretreated patients with multiple myeloma, as well as in combination with bortezomib in patients with newly diagnosed multiple myeloma.

Methods
In this phase 3 trial, we randomly assigned 498 patients with relapsed or relapsed and refractory multiple myeloma to receive bortezomib (1.3 mg per square meter of body-surface area) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg per kilogram of body weight) (daratumumab group). The primary end point was progression-free survival.

Results
A prespecified interim analysis showed that the rate of progression-free survival was significantly higher in the daratumumab group than in the control group; the 12-month rate of progression-free survival was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median progression-free survival was not reached in the daratumumab group and was 7.2 months in the control group (hazard ratio for progression or death with daratumumab vs. control, 0.39; 95% confidence interval, 0.28 to 0.53; P<0.001). The rate of overall response was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, P<0.001), as were the rates of very good partial response or better (59.2% vs. 29.1%, P<0.001) and complete response or better (19.2% vs. 9.0%, P=0.001). Three of the most common grade 3 or 4 adverse events reported in the daratumumab group and the control group were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively). Infusion-related reactions that were associated with daratumumab treatment were reported in 45.3% of the patients in the daratumumab group; these reactions were mostly grade 1 or 2 (grade 3 in 8.6% of the patients), and in 98.2% of these patients, they occurred during the first infusion.

Conclusion
Among patients with relapsed or relapsed and refractory multiple myeloma, daratumumab in combination with bortezomib and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone and was associated with infusion-related reactions and higher rates of thrombocytopenia and neutropenia than bortezomib and dexamethasone alone. (Funded by Janssen Research and Development; ClinicalTrials.gov number, NCT02136134.)

3.2 Bortezomib (Velcade®) with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant

Overview

Drug Description	a first-in-class proteasome inhibitor
Patient Indication	bortezomib with lenalidomide and dexamethasone for untreated multiple myeloma who were not planned for immediate autologous stem-cell transplant
Incidence in Austria	382 newly diagnosed per year (2014), 4.3/100,000/year (European Standard Population, 2013)

Ongoing Phase III		NCT02136134 - until 03/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	12/2013: monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. 08/2008: in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high dose chemotherapy with haematopoietic stem cell transplantation. 06/2013: in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation. 01/2015: in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.
	FDA	06/2003: for the treatment of patients with multiple myeloma 12/2006: for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Costs		1 cycle → 21 days Dexamethasone: in one treatment cycle a dosis of 20 mg was administered 8 times → total of 160 mg; 100 mg → €28.70 and for 160 mg costs of €45.92 would incur for 1 treatment cycle Bortezomib: 1.3 mg/square meter body surface administered (subcutaneously) 4 times per treatment cycle; 3.5 mg → €1,218.95 assuming a body surface of 1.70 m^2, 2.21 mg (€769.68) are needed per administration and for 1 treatment cycle costs of €3,078.7 would incur Lenalidomide: 1 cycle: 25 mg daily on days 1–14; 21 pieces → €6,696.10 and for 1 treatment cycle (14 pieces) €4,464.1 would incur Total costs of €7,588.72 for 1 treatment cycle of combination treatment would incur

Phase III results

Lancet (2016) published online December 22, (Durie et al.): *"Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial"*

Background
Lenalidomide plus dexamethasone is a reference treatment for patients with newly diagnosed myeloma. The combination of the proteasome inhibitor bortezomib with lenalidomide and dexamethasone has shown significant efficacy in the setting of newly diagnosed myeloma. We aimed to study whether the addition of bortezomib to lenalidomide and dexamethasone would improve progression-free survival and provide better response rates in patients with previously untreated multiple myeloma who were not planned for immediate autologous stem-cell transplant.

Methods
In this randomised, open-label, phase 3 trial, we recruited patients with newly diagnosed multiple myeloma aged 18 years and older from participating Southwest Oncology Group (SWOG) and National Clinical Trial Network (NCTN) institutions (both inpatient and outpatient settings). Key inclusion criteria were presence of CRAB (C=calcium elevation; R=renal impairment; A=anaemia; B=bone involvement) criteria with measurable disease (measured by assessment of free light chains), Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, haemoglobin concentration 9 g/dL or higher, absolute neutrophil count 1 × 103 cells per mm3 or higher, and a platelet count of 80 000/mm3 or higher. We randomly assigned (1:1) patients to receive either an initial treatment of bortezomib with lenalidomide and dexamethasone (VRd group) or lenalidomide and dexamethasone alone (Rd group). Randomisation was stratified based on International Staging System stage (I, II, or III) and intent to transplant (yes vs no). The VRd regimen was given as eight 21-day cycles. Bortezomib was given at 1·3 mg/m2 intravenously on days 1, 4, 8, and 11, combined with oral lenalidomide 25 mg daily on days 1–14 plus oral dexamethasone 20 mg daily on days 1, 2, 4, 5, 8, 9, 11, and 12. The Rd regimen was given as six 28-day cycles. The standard Rd regimen consisted of 25 mg oral lenalidomide once a day for days 1–21 plus 40 mg oral dexamethasone once a day on days 1, 8, 15, and 22. The primary endpoint was progression-free survival using a prespecified one-sided stratified log rank test at a significance level of 0·02. Analyses were intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00644228.

Findings
Between April, 2008, and February, 2012, we randomly assigned 525 patients at 139 participating institutions (264 to VRd and 261 to Rd). In the randomly assigned patients, 21 patients in the VRd group and 31 in the Rd group were deemed ineligible based mainly on missing, insufficient, or early or late baseline laboratory data. Median progression-free survival was significantly improved in the VRd group (43 months vs 30 months in the Rd group; stratified hazard ratio [HR] 0·712, 96% CI 0·56–0·906; one-sided p value 0·0018). The median overall survival was also significantly improved in the VRd group (75 months vs 64 months in the Rd group, HR 0·709, 95% CI 0·524–0·959; two-sided p value 0·025). The rates of overall response (partial response or better) were 82% (176/216) in the VRd group and 72% (153/214) in the Rd group, and 16% (34/216) and 8% (18/214) of patients who were assessable for response in these respective groups had a complete response or better. Adverse events of grade 3 or higher were reported in 198 (82%) of 241 patients in the VRd group and 169 (75%) of 226 patients in the Rd group; 55 (23%) and 22 (10%) patients discontinued induction treatment because of adverse events, respectively. There were no treatment-related deaths in the Rd group, and two in the VRd group.

Interpretation
In patients with newly diagnosed myeloma, the addition of bortezomib to lenalidomide and dexamethasone resulted in significantly improved progression-free and overall survival and had an acceptable risk-benefit profile.

4 Skin cancer

4.1 Prolonged survival in stage III melanoma with ipilimumab (Yervoy®) adjuvant therapy

Overview

Drug Description	a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4) to augment antitumor immune responses
Patient Indication	ipilimumab indicated at a dose of 10 mg per kilogram in patients who had undergone complete resection of stage III melanoma
Incidence in Austria	1,794 newly diagnosed per year (2014), 21.1 /100,000/year (European Standard Population, 2013)
Ongoing Phase III	NCT00636168 - until 09/2019

Approval status for this indication	**EMA**	-
	FDA	10/2015: Approval for the additional indication of adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
Approval status for other indications	**EMA**	03/2011: Approval for the treatment of unresectable or metastatic melanoma in adults who have received prior therapy
	FDA	approval status 2011: indicated for the treatment of unresectable or metastatic melanoma
Costs		YERVOY 1 cycle → 21 days The recommended dose-schedule of ipilimumab is 10 mg/kg intravenously every 3 weeks for 4 doses, thereafter every 3 months for up to 3 years; 5mg/ml 10 ml → €4,447.45; assuming an average body weight of 70 kg, a dose of 700 mg iplimumab would be needed, costing €62,264.30 per a 3-week cycle

Phase III results

N Engl J Med 2016; 375:1845-1855, (Eggermont et al.) *"Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy"*

Background
On the basis of data from a phase 2 trial that compared the checkpoint inhibitor ipilimumab at doses of 0.3 mg, 3 mg, and 10 mg per kilogram of body weight in patients with advanced melanoma, this phase 3 trial evaluated ipilimumab at a dose of 10 mg per kilogram in patients who had undergone complete resection of stage III melanoma.

Methods
After patients had undergone complete resection of stage III cutaneous melanoma, we randomly assigned them to receive ipilimumab at a dose of 10 mg per kilogram (475 patients) or placebo (476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred. Recurrence-free survival was the primary end point. Secondary end points included overall survival, distant metastasis–free survival, and safety.

Results
At a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (hazard ratio for recurrence or death, 0.76; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). The rate of overall survival at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (hazard ratio for death, 0.72; 95.1% CI, 0.58 to 0.88; P = 0.001). The rate of distant metastasis–free survival at 5 years was 48.3% in the ipilimumab group, as compared with 38.9% in the placebo group (hazard ratio for death or distant metastasis, 0.76; 95.8% CI, 0.64 to 0.92; P = 0.002). Adverse events of grade 3 or 4 occurred in 54.1% of the patients in the ipilimumab group and in 26.2% of those in the placebo group. Immunerelated adverse events of grade 3 or 4 occurred in 41.6% of the patients in the ipilimumab group and in 2.7% of those in the placebo group. In the ipilimumab group, 5 patients (1.1%) died owing to immune-related adverse events.

Conclusion
As adjuvant therapy for high-risk stage III melanoma, ipilimumab at a dose of 10 mg per kilogram resulted in significantly higher rates of recurrence-free survival, overall survival, and distant metastasis‑free survival than placebo. There were more immune-related adverse events with ipilimumab than with placebo. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00636168, and EudraCT number, 2007-001974-10.)

Lancet Oncol. 2017 Feb 2. pii: S1470-2045(17)30015-3. (Coens et al): *"Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial"*

Background
The EORTC 18071 phase 3 trial compared adjuvant ipilimumab with placebo in patients with stage III melanoma. The primary endpoint, recurrence-free survival, was significantly longer in the ipilimumab group than in the placebo group. Investigator-reported toxic effects of ipilimumab consisted mainly of skin, gastrointestinal, endocrine, and hepatic immune-related adverse events. Adjuvant treatment with ipilimumab in this setting was approved in October, 2014, by the US Food and Drug Administration based on the results of the primary outcome of this trial. Here, we report the results of the secondary endpoint, health-related quality of life (HRQoL), of this trial.

Methods:
EORTC 18071 was a multinational, double-blind, randomised, phase 3 trial in patients with stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis) in 19 countries worldwide. Participants were randomly assigned (1:1) centrally by an interactive voice response system, to receive either ipilimumab 10 mg/kg or placebo every 3 weeks for four doses, then every 3 months for up to 3 years. Using a minimisation technique, randomisation was stratified by disease stage and geographical region. HRQoL was assessed with the EORTC QLQ-C30 quality-of-life instrument at baseline, weeks 4, 7, 10, and 24, and every 12 weeks thereafter up to 2 years, irrespective of disease progression. Results were summarised by time-point and in a longitudinal manner in the intention-to-treat population. Two summary scores were calculated for each HRQoL scale: the average score reported during induction (ipilimumab or placebo at a dose of 10 mg/kg, administered as one single dose at the start of days 1, 22, 43, and 64−ie, four doses in 3 weeks), and the average score reported after induction. A predefined threshold of a 10 point difference between arms was considered clinically relevant. The primary HRQoL endpoint was the global health scale, with the predefined hypothesis of no clinically relevant differences after induction between groups. This trial is registered with EudraCT, number 2007-001974-10, and ClinicalTrials.gov, number NCT00636168.

Findings
Between July 10, 2008, and Aug 1, 2011, 951 patients were randomly assigned to treatment: 475 in the ipilimumab group and 476 in the placebo group. Compliance with completing the HRQoL questionnaire was 893 (94%) of 951 patients at baseline, 693 (75%) of 924 at week 24, and 354 (51%) of 697 at week 108. Patient mean global health scores during (77.32 [SD 17.36] vs 72.96 [17.82]; p=0.00011) and after induction (76.48 [17.52] vs 72.32 [18.60]; p=0.00067) were statistically significantly different between groups but were not clinically relevant. Mean global health scores differed most between the groups at week 7 (77 [SD 19] in the placebo group vs 72 [22] in the ipilimumab group) and week 10 (77 [20] vs 70 [23]). Mean HRQoL scores differed by more than 10 points at week 10 between treatment groups for diarrhoea (7.67 [SD 17.05] for placebo vs 18.17 [28.35] for ipilimumab) and insomnia (15.17 [22.53] vs 25.60 [29.19]).

Interpretation
Despite increased toxicity, which led to treatment discontinuation for most patients during the induction phase of ipilimumab administration, overall HRQoL, as measured by the EORTC QLQ-C30, was similar between groups, as no clinically relevant differences (10 points or more) in global health status scores were observed during or after induction. Clinically relevant deterioration for some symptoms was observed at week 10, but after induction, no clinically relevant differences remained. Together with the primary analysis, results from this trial show that treatment with ipilimumab results in longer recurrence-free survival compared with that for treatment with placebo, with little impairment in HRQoL despite grade 3–4 investigator-reported adverse events.